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Communities near toluene diisocyanate sources: an investigation of exposure and health

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Toluene diisocyanate (TDI) is a well-known cause of occupational asthma, but we know little about the potential for exposure and health effects among residents who live near facilities that release TDI. In the mid-1990's, the North Carolina Department of Health and Human Services and the Agency for Toxic Substances and Disease Registry investigated exposures to TDI and health outcomes in one community, which left some unanswered questions. This cross-sectional study evaluated the potential associations between living near a TDI source and the prevalence of three variables: asthma or asthma-like respiratory symptoms, antibodies specific to TDI, and verifiable levels of TDI in residential air. Results among North Carolina residents living near such facilities (five target communities) were compared with the results from residents living further away (five comparison communities). Overall, the prevalence of reporting either asthma or asthma-like respiratory symptoms was higher (odds ratio = 1.60; 95% confidence interval = 0.97–2.54) among residents in target communities than those in comparison communities. However, this difference was not statistically significant. Symptom prevalence varied greatly among the community populations. The prevalence of respiratory symptoms was higher near facilities with historically higher TDI emissions. Among the 351 participants who provided blood samples, only one had immunoglobulin G specific antibodies to TDI. This participant lived in a target area and may have had non-occupational exposure. TDI was detected at an extremely low level (1 ppt) in one of the 45 air samples from target communities. One ppt is one-tenth the EPA reference concentration. Overall, air sample and antibody test results are not consistent with recent or ongoing exposure to TDI.
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Introduction

Toluene diisocyanate (TDI) is an organic compound used in manufacturing polyurethane foam and certain other commercial applications. TDI causes occupational asthma, but there are relatively few studies of TDI exposure and health effects among the general population. It is a mucus membrane and skin irritant and can sensitize the respiratory tract. The mechanism of sensitization is not completely understood, but both humoral and cell-mediated immunity are thought to be involved (Baur et al., 1996).

When a North Carolina manufacturer introduced a new curing process for polyurethane foam in 1996, nearby residents expressed concern about noxious odors and the possibility of adverse health effects. State and federal agencies tested the ambient air and private wells surrounding the facility and issued several public health notices (ATSDR, 1997a, b, 1998).

The problems at this facility were resolved when the North Carolina State Health Director ordered it to close until it could operate without creating a public health nuisance. The situation led to concern that community exposure could be causing respiratory health problems around other facilities in North Carolina that emit TDI.

Although some occupational and community health studies have incorporated medical examinations to diagnose asthma, this approach is costly, time consuming, and may require more than one doctor/participant encounter for a diagnosis. However, there are validated questionnaires available to screen for asthma or asthma-like respiratory symptoms (Burney and Chinn, 1987; Burney et al., 1989; Abramson et al., 1991;

1. Abbreviations: CI, confidence interval; HDI, hexamethylene diisocyanate; IgE, immunoglobulin E; IgG, immunoglobulin G; LC-MS-MS, liquid chromatography, mass spectrometry, mass spectrometry; LOD, limit of detection; MDI, diphenylmethane diisocyanate; OR, odds ratio; ppb, parts per billion; ppt, part per trillion; TDI, toluene diisocyanate; TRI, Toxic Release Inventory

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Venables et al., 1993). The sensitivity and specificity of the Venables questionnaire varied with the precise health outcome assessed and number of symptoms reported. For a self-reported diagnosis of asthma, reporting two symptoms had a sensitivity of 91% and a specificity of 85%. For bronchial hyperresponsiveness, reporting two symptoms had a sensitivity of 79% and a specificity of 87% (Venables et al., 1993).

Numerous studies among workers have evaluated serum antibodies to diisocyanates as potential markers for exposure and asthma. The minimum time from TDI exposure to the presence of detectable antibodies is unknown. Once exposure ceases, the levels of serum antibodies specific to TDI tend to decrease over time. The reported half-lives range from 2.3 to 4.8 years for immunoglobulin E (IgE) and 1.1–6.7 years for immunoglobulin G (IgG) (Park et al., 2002; Malo et al., 2006). For this reason, higher titers are more likely to be associated with recent exposures than are lower titers.

Two studies conducted in the 1980 s found people without known exposure to be negative for diisocyanate-antigen specific IgE and IgG (Keskinen et al., 1988; Selden et al., 1989). A community investigation among people living near a manufacturing plant using TDI tested for diisocyanate antigen-specific IgG and IgE antibodies to assess exposure (CDC, 1998; Orloff et al., 1998). Some of the participants (9%; 10/113) had antibodies to one or more of the three diisocyanates: TDI, hexamethylene diisocyanate (HDI), or diphenylmethane diisocyanate (MDI). A similar investigation in the same community found positive antibody responses in 6 (18%) of 33 symptomatic residents evaluated (Darcey et al., 2002). However, these investigations were conducted in the 1990 s when inhibition testing to exclude false positives was not part of the laboratory analysis for diisocyanate antibodies. These investigations also lacked unexposed populations for comparison, making interpretation of the results difficult.

More recently, Bernstein et al. (2006) tested serum samples from 139 anonymous donors. The authors reported that these donors were unexposed, but did not provide the specifics of this determination. They found TDI specific antibodies in two participants (1%; 2/139) and HDI specific antibodies in six participants (4%; 6/139). The laboratory methodology was similar to that in the current investigation, requiring both elevated antibody levels and $>50\%$ inhibition with the specific antigen.

The purpose of this investigation was to evaluate the potential associations between living near a TDI emission source and three variables: asthma or asthma-like respiratory symptom prevelance, diisocyanate-specific antibodies, and verifiable levels of TDI in residential air.

Methods

Facility and Study Area Selection

We reviewed the quantities of TDI reported to the US Environmental Protection Agency's Toxic Release Inventory (EPA's TRI). We then ranked North Carolina facilities from highest to lowest emissions using a 7-year average of the releases from January 1998 to December 2004 (USEPA TRI, 2009). As MDI and HDI exposure may confound antibody and respiratory health results, we excluded facilities that reported emitting more than negligible amounts of HDI or MDI.

Beginning with the facility with the highest emission average, we toured the area to make sure that at least 25 homes were within an approximate $\frac{1}{4}$-mile radius from the facility property boundary and that there were no other diisocyanate emission sources (e.g., autobody paint shop) within a mile. This process was repeated until we reached the population size estimated to provide adequate statistical power. Areas around five separate TDI-emitting facilities were selected; all were polyurethane foam manufacturers.

Comparison areas were selected from the same North Carolina county as their respective target areas. US 2000 Census tract and block group data were used to characterize and match target and comparison communities by age, gender, race, and income. Like the target communities, we searched the TRI database and toured comparison areas to ensure no nearby sources of diisocyanate emissions were present. Finally the area needed at least 25 homes located within an approximate $\frac{1}{4}$-mile radius from a selected intersection.

Recruitment

To be eligible for the study, individuals had to reside in a target or comparison area for 1 year or longer, be at least 18 years of age, and report no occupational exposure to TDI or other diisocyanates. An attempt was made to identify and recruit all eligible subjects in all the target/comparison areas. Actions were taken to inform residents about the study before, during, and after completion of fieldwork. Outreach efforts to educate communities included public availability meetings, press releases, mailings, fact sheets, and door-to-door canvassing of selected communities. From May 2007 to January 2008, trained field staff canvassed neighborhoods to recruit eligible residents living in the five target and five comparison areas. There was no limit on the number of eligible participants per household that could enroll in the study.

The Institutional Review Boards at the Centers for Disease Control and Prevention and the North Carolina Division of Public Health approved the study protocol. Informed written consent was obtained from each individual before participation. Participants could consent to blood sampling or answering respiratory and demographic questions, or to both. Up to four residents per community provided written consent for air sampling equipment to be placed in their yards for a time period of 4 to 6 weeks.

Questionnaire

The questionnaire collected information on demographics, residential history, outdoor activities, asthma diagnoses, smoking history (e.g., cigarettes, cigars, and pipe smoking),

chronic health conditions (e.g., emphysema, congestive heart failure, chronic bronchitis, lung cancer, sarcoidosis, and scoliosis), and possible occupational and non-occupational exposure to diisocyanates.

The questionnaire also included the nine questions for asthma-like respiratory symptoms from Venables et al. (1993): 'During the past 4 weeks: If you run, or climb stairs fast do you ever …cough? …wheeze? …get tight in the chest? Is your sleep ever broken by …wheeze? …difficulty with breathing? Do you ever wake up in the morning (or from your sleep if a shift worker) with …wheeze? …tightness in the chest? Do you ever wheeze … if you are in a smoky room? …if you are in a very dusty place?'

Antibody Tests

Participants were asked to provide a blood sample to test for IgG and IgE antibodies specific to TDI, HDI, and MDI. Two 10 cc blood samples were collected and the serum was stored at 4°C for up to 3 days. The serum was shipped overnight with cold gel packs to the Allergy Diagnostic Laboratory in the Division of Allergy-Immunology at the University of Cincinnati College of Medicine for analyses.

Sera were tested for IgG and IgE antibodies specific to TDI, MDI, and HDI as previously described (Campo et al., 2007). The three co-authors affiliated with the University of Cincinnati College of Medicine performed and interpreted the antibody tests. Samples that showed binding with human serum albumin alone were classified as 'specific antibody negative.' Due to the relatively low optical density readings obtained in the enzyme linked immunosorbent assay screening tests, sera were considered positive only if the test was reproducible after repeating the test twice on two separate occasions. To avoid false positive results, the specificity of each positive antibody result was confirmed by antibody inhibition testing with diisocyanate antigens. Confirmed positive results for IgG or IgE antibodies demonstrated >50 percent inhibition to the specific antigen. Sera that failed to inhibit $\geq 50\%$ with diisocyanate antigens were defined as 'specific antibody negative.'

Air Sampling

In each of the target and comparison areas, four Zellweger Analytics Single Point Monitors tested the ambient air for TDI. These monitors were selected based on their ability to detect TDI at low concentrations in occupational settings. The monitors were placed in yards of residents in the study areas and ran 24 h per day for 4 to 6 weeks. For the real-time air monitors, the lower and upper limits of detection for diisocyanates were 2 and 60 parts per billion (ppb), respectively. If a monitor indicated that TDI was present, a time-weighted air sample was electronically triggered. An 8-h sample was initiated if the monitor detected 2 ppb or greater; a 15-min sample was also collected if 4 ppb or greater was detected. All samples activated by a monitor reading at or above 2 ppb were sent for laboratory analysis. To ensure that at least one air sample was collected at each monitoring location, one planned 8-h sample was collected. All planned samples were collected on the same day for each set of target and comparison communities. If no electronically triggered sample was collected at a sample location, the planned sample was sent for laboratory analysis. Field blanks were also sent for analysis.

Bureau Veritas North America, analyzed the samples with isocratic liquid chromatography with mass spectrometry detection (LC-MS-MS) using multiple reaction monitoring. Samples were analyzed using the National Institute for Occupational Health and Safety Method 5525 adapted for LC-MS-MS for both TDI isomers (NIOSH, 2003). LC-MS provides better sensitivity and specificity for the determination of TDI.

Given the unique requirements for monitoring outside a workplace setting, the stability of the impregnated filters was tested to verify the useful life of the reagent 1-(9-anthracenylmethyl)piperazine. Because of the possibility of photodegradation, filters were placed in opaque cassettes and replaced both every other day.

Samples were stored in the freezer up to 16 months. Stability tests for 2,4- and 2,6-TDI on the filters were done for up to an 18-month storage period and showed adequate recovery ($>70\%$).

Statistical Analysis

Bivariate analyses were used to evaluate differences in target *vs* comparison area responses to the survey questions. Specifically, the χ^2 test for independence and Fisher's exact test were used to assess differences in responses to categorical variables and the *t*-test was used to assess differences in responses to continuous variables.

The US Census Bureau noted that many United States residents see race and ethnicity as the same concept. As such, race/ethnicity items were not two distinct variables and were combined for analysis (Hispanic, White, Black, and other). The American Anthropological Association recommended to combine the 'race' and 'ethnicity' categories into one question as ''race/ethnicity'' for the 2010 US Census (American Anthropological Association, 1997).

Most questionnaire items were considered *a priori* to be possible confounders (age, race, ethnicity, gender, residential history, outdoor activities, smoking history, chronic health conditions, and possible occupational and non-occupational exposure to diisocyanates). Questionnaire items on smoking history were used to define smoking status in combination with 'Are there any smokers who live in your household who smoke inside your home or car?' Current smokers indicated that they currently smoke (cigarettes, cigars, and/or a pipe); former smokers indicated that they used to smoke but do not smoke now; second hand smoke indicates persons who never smoked but live with some who smokes inside the home or

car; and never indicates persons who never smoked and do not live with someone who smokes. Chronic disease affecting respiration indicates persons who reported to have emphysema, congestive heart failure, chronic bronchitis, lung cancer, sarcoidosis, or scoliosis.

Participants answering 'yes' to two or more of the nine respiratory health screening questions or 'yes' to 'Have you ever been told by a doctor that you had asthma?' were categorized as having 'asthma or asthma-like respiratory symptoms' (Venables et al., 1993). In the text that follows, the terms 'symptoms', 'symptomatic', and 'respiratory symptoms' mean two or more 'asthma or asthma-like respiratory symptoms' as defined by the Venables (1993) questionnaire. The odds of self-reported 'asthma or asthma-like respiratory symptoms' in the target population relative to the comparison population was examined using logistic regression.

Exploratory stepwise logistic regression analysis was performed to identify variables that significantly contributed to the respiratory outcome. After including group status (target *vs* comparison) in the model, both forward selection ($P = 0.25$ for entry and $P = 0.10$ to stay) and backward elimination ($P = 0.25$ to stay) techniques were used to examine the association between all possible confounders and the respiratory outcome. Age, smoking status and chronic disease affecting respiration were consistently, significantly associated with the respiratory outcome. Subsequent models which added the other possible confounders were further examined; these variables did not improve the fit of the logistic regression model and produced unreliable estimates.

The association of self-reported asthma and asthma-like respiratory symptoms and residential TDI exposures was examined using multivariate logistic regression, controlling for age, smoking status, chronic disease affecting respiration, and study area. Given the heterogeneity among communities, facility/study area was inserted in the multivariate model as a dummy variable using target area E with the lowest average TDI release as the referent. Age, smoking status and chronic disease affecting respiration were also used in the site-specific population models. SAS version 9.1.3 for Windows was used for analysis (SAS Institute, 2004).

Results

Population Characteristics

A total of 384 people from 250 households completed the questionnaire. Based on questionnaire items, 20 of these participants were excluded from the analysis: one participant's date of birth indicated 11 years of age, two participants did not provide date of birth, which was needed to determine age, two had lived in the residential area less than 1 year, and 15 reported potential occupational exposure to TDI. Data from 364 participants from 239 households were included in the data analyses.

Most ($n = 143$, 59%) households contributed only one participant, but 32% ($n = 78$) had two participants and the remaining 9% ($n = 22$) of households had from three to seven participants. To obtain a household participation rate, the number of households with one or more eligible participant was divided by the total number of households identified in the US Census for the respective areas. This resulted in an overall household participation rate of 27% (118/442) for the target population and 23% (125/534) for the comparison group. Household participation rates varied among the five site-specific areas (82% target, 70% comparison for area A to 14% target, 18% comparison for area B).

Table 1 compares selected characteristics of the aggregate target and aggregate comparison populations. The two populations were similar regarding gender, the prevalence of chronic respiratory illness, and smoking status. The target population had a greater percentage of Hispanics and fewer African Americans. The comparison population had a slightly higher mean age and reported more non-occupational exposure to diisocyanates.

Aggregate Respiratory Symptoms

Stepwise logistic regression models consistently identified smoking status, chronic respiratory illness, and age as significant variables related to asthma or asthma-like symptoms (Table 2). Adjusting for these potential confounders in the statistical analysis resulted in an adjusted odds ratio (OR_a) of 1.60 (95% confidence Interval (CI) 0.97–2.54). Although not statistically significant, the OR suggests that more participants living in target areas reported more respiratory symptoms than participants living in the comparison areas.

Site-Specific Respiratory Symptoms

In addition to comparing the aggregate target and comparison populations, we also compared the individual target and comparison groups by site (Table 3). There was wide variability in the prevalence of respiratory symptoms reported by the various community populations. The proportion of target area participants reporting respiratory symptoms was higher at three sites (A, C and E). The difference was statistically significant ($P < 0.05$) for site A. The adjusted OR for site A was 5.49 (95% CI 1.70–17.72).

Antibodies

A total of 351 study participants (96%) (161 in target areas and 190 in comparison areas) provided a blood sample to test for IgG and IgE antibodies specific to TDI, HDI, and MDI. Table 4 displays details of the results. Seventeen persons (4.8%) had a positive antibody response to one of the diisocyanates. Five participants with positive results lived in

Table 1. Aggregate target *vs* comparison population characteristics.

Characteristic	Target areas ($N=166$)[a] N (%)	Comparison areas ($N=198$)[a] N (%)	P-value
Male	71 (42.8)	89 (44.9)	0.68
Race/ethnicity			
White	119 (71.7)	134 (67.7)	<0.0001
Black	11 (6.6)	48 (24.2)	
Hispanic	30 (18.1)	12 (6.1)	
Other	5 (3.0)	4 (2.0)	
Missing	1 (0.6)	0 (0.0)	
Smoking status[b]			
Current	39 (23.2)	52 (26.3)	0.66
Former	34 (20.5)	48 (24.2)	
Second hand	11 (6.6)	12 (6.1)	
Unexposed	82 (49.4)	86 (43.4)	
Chronic disease affecting respiration[c]	17 (10.2)	22 (11.1)	0.79
Non-occupational exposure[d]	26 (15.7)	48 (24.2)	0.04
Age, years			
Mean (SD)	43.0 (17.4)	47.7 (17.6)	0.01
Min and max	18–92	18–88	
Years at residence[e]			
Mean (SD)	12.9 (14.9)	15.3 (15.9)	0.13
Min and max	1–69	1–80	

[a]In all 20 of the 384 people did not meet participation criteria and were removed from analyses.
[b]Includes cigarettes, cigars, and pipe smoking.
[c]Includes emphysema, congestive heart failure, chronic bronchitis, lung cancer, sarcoidosis, and scoliosis.
[d]Exposure to TDI, HDI, or MDI that did not occur at work.
[e]Years of residence at the current location.

target areas; 12 lived in comparison areas. No participant had both IgG and IgE antibodies to the same diisocyanate and none had specific antibodies to more than one diisocyanate.

One participant had IgG antibodies specific to TDI and another had IgG antibodies specific to MDI. Fifteen participants had HDI-specific antibodies (13 IgG, two IgE). The participant with IgG antibodies specific to TDI lived in a target area and reported non-occupational exposure to diisocyanates. This individual did not have physician-diagnosed asthma or respond 'yes' to any of the nine respiratory health symptoms. Also, this participant had never smoked and did not have any chronic respiratory health conditions.

Two of the five target area participants with diisocyanate antibodies (40%) and four of the 12 comparison area participants with diisocyanate antibodies (33%) reported non-occupational exposure to diisocyanates. The exposure sources for these individuals included spray foam, deck sealant, and auto paint.

Table 2. Adjusted odds ratios for asthma or asthma-like symptoms (or both) by study population and other significant independent variables.

Characteristic	P-value	Odds ratio (95% CI)
Target *vs* comparison areas	0.07	1.6 (0.97, 2.54)
Chronic disease affecting respiration	<0.0001	5.45 (2.33, 12.76)
Smoking status[a]		
Former *vs* never	0.71	1.12 (0.60, 2.08)
Current *vs* never[b]	<0.001	2.87 (1.63, 5.05)
Site		
A *vs* E	0.12	1.85 (0.85, 4.04)
B *vs* E	0.18	0.56 (0.24, 1.31)
C *vs* E	0.14	1.83 (0.82, 4.08)
D *vs* E	0.81	1.10 (0.49, 2.46)
Age, years[c]	0.02	1.02 (1.00, 1.03)

[a]A few persons in the 'Never' smoke category had second hand exposure.
[b]'Current' smokers were more likely than 'Never' smokers to have 'asthma or asthma-like symptoms'.
[c]A continuous variable.

Air Monitoring and Sampling

Every target and comparison community had one or more electronically initiated air sample. Samples collected due to obvious monitor or electrical malfunction were not sent for laboratory analysis. A total of 108 samples were analyzed: 50 air samples initiated by real-time monitors, 29 planned 8-h air samples, and 29 quality control field blanks. Target area samples included 29 initiated by real-time monitors and 16-planned 8-h samples; comparison area samples included 21 initiated by real-time monitors and 13 planned samples.

Reviewing the initial results, the laboratory personnel noted that there was a positive detector response in one sample (target area C) at the correct retention time for both isomers (2, 4- and 2, 6-TDI). These responses were below the limit of detection (LOD) of 3 ng per sample. The laboratory then concentrated all samples by a factor of 10 to confirm that TDI isomers were present and to see if TDI was detectable in any other sample after concentration. The new estimated LOD and limit of quantitation in the concentrated samples was 0.5 and 1.7 ng, respectively, for both isomers. Average recoveries were between 92% and 107% for 2,4-TDI and between 96% and 103% for 2,6-TDI.

After the 10-fold concentration, TDI was found above the calculated LOD in three samples. Two of the three samples were from comparison area E. These two samples included a field blank (0.59 ng 2,4-TDI) and an 8-h sample (0.51 ng 2,4-TDI). Field blank contamination indicates an unknown contaminant source. There is no reason to believe that the TDI in the air sample is anything other than the contaminant found in the field blank.

The third sample containing TDI above the calculated LOD was from target area C. An 8-h sample contained both 2,4- and 2,6-TDI isomers for a total of 3.4 ng or $\sim$1 part per

Table 3. Site-specific participation rates and odds of reporting asthma-like symptoms[a] in individual target populations *vs* corresponding comparison areas.

Facility/study area	Household participation rate	Reported symptoms[a]		Odds of symptoms[a] in target *vs* comparison OR_a[b] (95% CI)	Annual ave TDI release[c] (lb/yr) 1998–2007	Air sample results (ppt)
		Yes *N* (%)	No *N* (%)			
A						
Target	80% (16/20)	17 (74)	6 (26)	5.49[d] (1.70–17.72)	320–80	ND
Comparison	70% (39/56)	25 (39)	39 (61)			
B						
Target	14% (23/167)	4 (11)	32 (89)	0.36 (0.09–1.37)	140–12	ND
Comparison	18% (28/153)	11 (27)	30 (73)			
C						
Target	67% (31/46)	25 (58)	18 (42)	2.47 (0.89–6.87)	498–564	1.0
Comparison	57% (13/23)	10 (34)	19 (66)			
D						
Target	22% (27/125)	10 (29)	25 (71)	0.53 (0.16–1.75)	180–255	ND
Comparison	14% (29/203)	19 (46)	22 (54)			
E						
Target	22% (18/82)	15 (52)	14 (48)	1.63 (0.44–6.06)	102–4	ND
Comparison	15% (15/98)	9 (39)	14 (61)			

Abbreviation: ND, not detected
[a]Asthma and/or asthma-like symptoms.
[b]OR_a = Odds ratio adjusted for chronic respiratory illness, smoking status, and age.
[c]As reported to the EPA Toxic Release Inventory.
[d]Statistically significant at $P \leq 0.05$.

Table 4. Positive results for IgG and IgE antibodies specific to TDI, HDI, and MDI in target *vs* comparison communities[a].

	Target ($N = 161$)	Comparison ($N = 190$)
IgG positive		
TDI	1	0
MDI	1	0
HDI	2[b]	11[c]
IgE positive		
TDI	0	0
MDI	0	0
HDI	1	1

[a]No participant tested positive for more than one diisocyanate-specific antibody, or for both IgG and IgE.
[b]One participant reported non-occupational exposure.
[c]Four participants reported non-occupational exposure.

trillion (ppt). This sample was collected at the edge of the recruitment area ($\sim\frac{1}{4}$-mile from the facility boundary). In addition, after concentration, positive detector responses at the correct retention times for both TDI isomers were noted in another 8-h sample from the same location, but are not reportable as they were both below the calculated LOD. Confirmatory peaks were also observed indicating a likelihood that the responses did in fact represent 2, 4- and 2,6-TDI.

Discussion

Respiratory Symptoms

We did not find compelling evidence of current TDI exposure among the target populations. Although self-reported asthma and asthma-like respiratory symptoms were more common in the aggregated target population, the difference between target and comparison populations (overall) was not statistically significant. Any differences between aggregate target and aggregate comparison groups do not appear to be related to recent or ongoing TDI exposure. Respiratory symptoms may result from a wide variety of environmental, occupational, and personal factors.

The community living near facility A had a significantly higher prevalence of symptoms than the corresponding comparison population (OR = 5.40, 95% CI = 1.70–17.72). This facility had the second highest historical emissions (Table 3). Facility C reported the highest past and current emissions. Although not statistically significant, participants near this facility reported respiratory symptoms more often than the corresponding comparison area participants. The past emissions for the remaining three facilities were much lower than those of facilities A and C.

TDI Antibodies

The presence of diisocyanate antibodies does not establish or rule out disease. Testing for diisocyanate antibodies is one

component in evaluating group exposure, especially in occupational settings. Antibody results are harder to interpret for individuals. Based on the antibody testing, this study did not find credible evidence of recent or ongoing exposure to TDI. As levels of these antibodies usually decrease over time, these results may not accurately reflect exposure in previous years, when the amount of TDI released was higher for most of the facilities.

Other Diisocyanate Antibodies

MDI and HDI antibodies were found at relatively equal prevalence in participants from both target and comparison communities. Of the 17 participants testing positive, ~one-third reported non-occupational exposures to diisocyanates. These results suggest that non-occupational exposures may be occurring due to the use of consumer products containing diisocyanates (e.g., spray foam insulation, glues, etc.). There is a need to study the relationships between diisocyanates other than TDI and respiratory health in the general population.

Air Monitoring and Sampling

The 2,4-TDI level from target area C may be biased (high) because of the contamination seen in the field blank. Although the level of 2,4-TDI in this target area sample could be explained by the possibility of contamination as seen in the blank sample, the additional presence of the 2,6-TDI isomer in the area C sample adds credence that these responses are in fact 2,4- and 2,6-TDI.

Given that laboratory analysis detected both 2,4- and 2,6-TDI isomers and at a value much lower than the LOD of the air monitors (2 ppb), it seems obvious that the real-time monitors yielded false positive results throughout the study. Twenty-nine air samples were triggered by air monitors when TDI was detected at 2 ppb or above in the target communities; 21 samples were triggered in the comparison communities. The air monitors indicated TDI present at concentrations from 2 to 60 ppb. The potential impact of many environmental variables on the false-positive results in target and comparison areas is under investigation. Potentially problematic factors include temperature, dew point, humidity, and other ambient air pollutants.

North Carolina industries are required to meet the 24-h acceptable ambient level (30 ppt) for TDI at their property boundaries (NCDNER, 1997). This level does not preclude minute concentrations beyond facility boundaries, as occurred in target area C. However, it is interesting to note that among the five facilities studied during 2007, the facility associated with the positive sample (facility C) also reported more pounds (lbs) of released TDI (564 lbs) than the other four facilities combined (351 lbs).

Limitations

Although aggregating the target and comparison populations was necessary to increase the study's power to detect associations, this also led to limitations. The facilities varied by the amount of TDI released. The average length of residence in the target communities also varied. Homes in target area B were built in 2002, providing fewer years and possibly relatively lower levels of potential exposure. Further, the socioeconomic status of participants from target area B was higher than those from comparison area B. Factors like these can introduce bias into the analyses.

Another limitation is related to the unexpectedly high prevalence (37%) of self-reported asthma or asthma-like respiratory symptoms in the comparison population. Although validated in a group of London office workers, the questionnaire from Venables et al. (1993) may have reduced specificity for asthma in our study population. The population of London office workers was probably healthier than our study participants from North Carolina's general population. For example, the office workers may have lower rates of chronic obstructive respiratory diseases that interfere with breathing in ways similar to asthma. Individuals with such diseases are likely to be identified as symptomatic when using the Venables et al. (1993) questionnaire.

In addition, the Venables questions may be interpreted by interviewers and those interviewed to apply to either the 'last four weeks' or to any time in your life ("do you ever"). For any particular participant, it isn't possible to know exactly the time period on which the response was based. However, the Venables questions were used in both the target and comparison areas; therefore, any inherent misclassification would be non- differential. The method used to identify asthma-like symptoms among adults should be improved and validated in a population more similar to the one studied.

Public Health Considerations

Although the aggregate data did not find a statistical association between the prevalence of respiratory symptoms and living near a facility releasing TDI, there were site-specific differences that warrant further investigation. For example, the prevalence of respiratory symptoms was elevated in three target areas; for one, the elevation was statistically significant. Based on data submitted to the EPA TRI, two of the facilities (A and C) have the highest historical emissions and one (C) remains the highest emitter. In addition, airborne TDI (1 ppt) was detected ~1/4 mile from facility C. Although no compelling statistical associations can be drawn between the prevalence of respiratory symptoms and exposure to TDI, further review of facility A and C emissions is warranted from a public health perspective.

Conclusions

This study resulted in three separate conclusions. First, although differences in respiratory symptoms might be

related to historical emission levels, they seem unlikely overall to be related to recent or ongoing exposures to TDI. Next, the presence of antibodies for diisocyanate in both target and comparison communities suggest that non-occupational exposures may be occurring from the use of diisocyanate-containing consumer products. Finally, the real-time air monitoring technology used to measure TDI was not reliable in an outdoor environment.

Next steps

State regulatory agencies will reevaluate the air modeling and operating permit for facilities A and C. In addition, the following research is recommended: the method used to identify asthma-like symptoms among adults should be improved and validated in a population more similar to the one studied. There is also a need to study the relationships between diisocyanates other than TDI and respiratory health in the general population. Finally, environmental factors influencing real-time TDI air monitor reliability need investigation.

Conflict of interest

The authors declare no conflict of interest.

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